A REVIEW OF EVIDENCE ON

THE JOINT RELATIONSHIP

OF ASBESTOS EXPOSURE AND SMOKING

TO RISK OF

LUNG CANCER

Author: P N Lee

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EXECUTIVE SUMMARY

Evidence on the joint relationship of asbestos exposure and smoking to risk of lung cancer is reviewed. Twenty-two studies that provided relevant information were identified. These included occupational studies of miners and millers of asbestos, asbestos products workers, insulation workers, asbestos sprayers and asbestos-exposed electrochemical workers, studies of asbestosis and silicosis patients, and case-control studies conducted in railroad workers and in shipbuilding and industrial areas.

The evidence, taken as a whole, has a number of limitations, including small numbers of lung cancers in many of the studies, particularly in nonsmokers, unreliable assessment of asbestos exposure, unvalidated smoking data, frequent reliance on death certificate diagnosis, reliance on data from proxy respondents in some studies and little consideration of other lung cancer risk factors.

Despite these limitations, the data allow a number of main conclusions to be drawn:

(i) Asbestos exposure does increase risk of lung cancer in those who have never smoked.

(ii) The joint relationship of asbestos exposure and smoking to risk of lung cancer is not well explained by the additive model. This risk in smokers exposed to asbestos is, in virtually every study, more than would be expected based on the increases in risk associated with smoking only and with asbestos exposure only.

(iii) The joint relationship is well explained by the multiplicative model, i.e. the increase in risk associated with asbestos exposure can be taken to be the same in smokers and in those who have never smoked.

TABLE 4.1 The 22 studies

Study author*	Study population	Location	Design	Mortality follow-up**	Date smoking habits obtained
DEKLERK	Crocidolite miners and millers	Wittenoom, Australia	Occupational (with nested case-control)	1979-91	1979
NEUBERGER	Asbestos cement products workers	Vöcklabruck, Austria	Occupational	1950-87	1982†
LIDDELL	Chrysotile miners and millers	Quebec, Canada	Occupational (with nested case-control)	1950-92	1970
CHENG	Chrysotile asbestos products workers	Tianjin, China	Occupational	1972-??	1972
HUILAN	Chrysotile asbestos products workers	8 factories, China	Occupational	1972-86	1972
BERRY	Asbestos factory workers	E. London, England	Occupational	1960-80	1971
ACHESON	Amosite asbestos factory workers	Uxbridge, England	Occupational	1947-79	1971
MARTISCHNIG	Hospital patients in shipbuilding area	Gateshead, England	Case-control	1972-73	1972-73†
OKSA	Asbestos sprayers, asbestosis and silicosis patients	Finland	Cohort of identified groups	1967-94	1987 (sprayers), 1977-85 (patients)
MEURMAN	Anthophyllite miners	N. Savo, Finland	Occupational, (with nested case-control)	1953-91	1967
RUBINO	Chrysotile miners and millers	Balangero, Italy	Occupational (with nested case-control)	1946-75	~1976†
PASTORINO	Hospital patients and general population in industrial areas	Lombardy, Italy	Case-control	1976-79	>1979†
MINOWA	Decedents in shipbuilding area	Yokosuka, Japan	Case-control	1978-82	>1982†
KJUUS	Hospital patients in industrial and shipbuilding areas	Telemark and Vestfold, Norway	Case-control	1979-83	1979-83†

TABLE 4.1 The 22 studies
(contd.)

Study author*	Study population	Location	Design	Mortality follow-up**	Date smoking habits obtained
HILT	Workers in nitric acid production plant	Telemark, Norway	Occupational	1953-80	?
ELMES	Insulation workers	Belfast, N. Ireland	Occupational	1940-66	?
HUGHES	Asbestos cement product workers	New Orleans, USA	Occupational	1969-83	1969
SELIKOFF 1	Amosite asbestos factory workers	New Jersey, USA	Occupational	1961-77	1961
SELIKOFF 2	Insulation workers	New York and New Jersey,USA	Occupational	1943-74	1962
HAMMOND	Insulation workers	USA and Canada	Occupational	1967-76	1967
GARSHICK	Decedent railroad workers	USA	Case-control	1981-82	>1982†
BLOT	Hospital patients and decedents in shipbuilding areas	4 states, USA	Case-control	1970-78	1970-78†

* First author of paper or of main paper where multiple publications; see sections 3.2-3.23 for fuller details of the studies

** Or period of hospitalization or death for case-control studies

† Data obtained after death or diagnosis

TABLE 4.2 Lung cancer deaths and cases

Study author	Deaths or cases	Source of diagnosis	Number of deaths/cases	
			Total	With smoking data
DEKLERK	Deaths	Death certificates	71	40
NEUBERGER	Deaths	Death certificates and medical records	50	≤50
LIDDELL	Deaths	Death certificates	657	299
CHENG	Deaths	Death certificates (?)	21	≤21
HUILAN	Deaths	Death certificates (?)	67	57
BERRY	Deaths	Death certificates	123	79
ACHESON	Deaths	Death certificates	71	26
MARTISCHNIG	Cases	Firm diagnosis by radiography, bronchoscopy or thoracotomy	201	201
OKSA	Cases	Cancer registration	58	51
MEURMAN	Cases	Cancer registration	77	55
RUBINO	Deaths	Death certificates and medical records	12	12
PASTORINO	Cases	Hospital diagnosis and review of medical records	204	176
MINOWA	Deaths	Confirmed by cytology, surgical specimens or autopsy	96	96
KJUUS	Cases	Hospital diagnosis	176	176
HILT	Deaths	Death certificates	13	9
ELMES	Deaths	Death certificates and medical records	28	19
HUGHES	Deaths	Death certificates	29	29
SELIKOFF 1	Deaths	Death certificates and medical records	60	60
SELIKOFF 2	Deaths	Death certificates and medical records	89	47
HAMMOND	Deaths	Death certificates and medical records	450	276
GARSHICK	Deaths	Death certificates	1256	1081
BLOT	Deaths and cases	Death certificates and hospital diagnosis	~1100*	~1100*

† There were a total of 1072 cases in 3 of the sub-studies; with a combined total of 64 cases and controls in the fourth sub-study

TABLE 4.3 Source of asbestos and smoking data

Study author	Source of asbestos exposure	Risk related to exposure*	Source of smoking data
DEKLERK	Work history and dust measurements	Measured	Questionnaire to workers
NEUBERGER	Work history and dust measurements	Broad	Questionnaire to living workers or proxies for decedents
LIDDELL	Work history and dust measurements	Measured	Questionnaire to living workers or proxies for decedents
CHENG	Work history and dust measurements	Broad	Questionnaire to workers (?)
HUILAN	Work history and dust measurements	Yes/No	Questionnaire to workers (?)
BERRY	Work history (?)	Broad	Questionnaire or interview with workers
ACHESON	Work history and dust measurements	Broad	Medical interview with workers
MARTISCHNIG	Questionnaire re work history and asbestos exposure; fibre counts in long tissue of cases	Yes/No	Medical interview with patients
OKSA	Medical interview with subjects	External	Medical interview with subjects
MEURMAN	Work history	Broad	Questionnaire to workers
RUBINO	Work history and dust measurements	Measured	Interviews with living workers or proxies for decedents
PASTORINO	Interview of subjects and proxies re work history	Yes/No	Interview with subjects or proxies
MINOWA	Interview of proxies re work history	Broad	Interview with proxies
KJUUS	Interview with patients re asbestos exposure	Broad	Interview with patients
HILT	Work history	Broad	Various unspecified sources
ELMES	Inferred from nature of population studied	External	Interview with living workers and search of hospital and work records for decedents
HUGHES	Work history and dust measurements	Measured	Interview with workers
SELIKOFF 1	Inferred from nature of population studied	External	Questionnaire to workers
SELIKOFF 2	Inferred from nature of population studied	External	Interview with workers
HAMMOND	Inferred from nature of population studied	External	Questionnaire to workers

TABLE 4.3 Source of asbestos and smoking data (cont'd)

Study author	Source of asbestos exposure	Risk related to exposure*	Source of smoking data
GARSHICK	Work history	Yes/No	Questionnaire to proxies
BLOT	Interview with patients or proxies re work history	Yes/No**	Interview with patients or proxies

* Results presented by either measured category of asbestos exposure, broad category (e.g. heavy, medium, light), or simply by whether exposure occurred or not (yes/no). In 5 studies, risk was not related to level of exposure within the study population, risk for the whole population being compared to an external population

** Yes/No for BLOT refers to ever employed in shipbuilding

TABLE 4.4 Potential confounding variables taken into account by matching, confounding adjustment or in the SMR calculations

	Variables taken into account in		
Study author	Matching	Adjustment	SMR calculations
DEKLERK	Age	None	-
NEUBERGER	-	None	Age, period, region
LIDDELL	Date of birth, age of starting work, period of employment	None	Age, period, region
CHENG	-	Age	Age, period, region
HUILAN	-	Not stated	-
BERRY	-	None	Age, period, region, availability of smoking data
ACHESON	-	None	Age, period, country
MARTISCHNIG	Age, catchment area	None	-
OKSA	-	None	Age, period, country
MEURMAN	Date of birth, vital status, date of death	None	Age, period, region
RUBINO	Date of birth	None	-
PASTORINO	Age	PAH*	-
MINOWA	Date of birth	Age	-
KJUUS	Age	None	-
HILT	-	Age	-
ELMES	-	None	Age, period, country
HUGHES	-	None	Age, period, region
SELIKOFF 1	-	None	Age, period, country**
SELIKOFF 2	-	None	Age, period, country
HAMMOND	-	None	Age, period, country**
GARSHICK	Date of birth, date of death	Age, diesel-years	-
BLOT	Age, race, hospital, county of residence	None	-

* Exposure to polycyclic aromatic hydrocarbons at work

** Comparisons were made with a group of white men who were not farmers, had no more than high school education and had a history of occupational exposure to dust, fumes, vapours, gases, chemicals or radiation

TABLE 5.3 Validity of additive model

Study	Sum of risks for A^-S^- and A^+S^+	Sum of risks for A^-S^+ and A^+S^-	Difference
DEKLERK	10.57	5.68	4.89
MARTISCHNIG	6.57	2.86	3.71
RUBINO*	2.32	1.00	1.32
PASTORINO (no PAH)	10.86	8.29	2.57
PASTORINO (PAH)	16.50	9.14	7.36
KJUUS	20.90	7.82	13.08
BLOT (Georgia)	8.58	5.99	2.59
BLOT (Virginia)	5.87	4.97	0.90
BLOT (Florida)	8.79	7.81	0.98
CHENG	9.43	7.01	2.42
HUILAN	12.06	5.61	6.45
LIDDELL	2.04	2.26	-0.22
ACHESON	2.10	0.90	1.20
MEURMAN	4.16	4.13	0.03
OKSA (Asbestos sprayers)**	11.37	1.07	10.30
OKSA (Asbestosis patients)**	12.41	1.07	11.34
OKSA (Silicosis patients)**	3.50	1.07	2.43
SELIKOFF 2**	11.21	2.34	8.87
BERRY (Men)†	4.40	1.73	2.67
BERRY (Women)†	5.10	2.25	2.85
SELIKOFF 1†,**	5.17	4.82	0.35
HILT	26.16	5.84	20.32
HAMMOND	54.24	16.02	38.22

* Risk relative to A^-S^+

** Assuming SMR in A^-S^- is 0.15 and in A^-S^+ is 1.07

† Dividing smoking specific expected values by 0.15 for S^- and 1.07 for S^+ to make them comparable to the same reference population

TABLE 5.4 Validity of multiplicative model

Study*		Product of risks for A^-S^- and A^+S^+	Product of risks for A^-S^+ and A^+S^-	Ratio = U
DEKLERK		9.57	7.71	1.24
MARTISCHNIG		5.57	1.92	2.90
RUBINO		0.00	0.00	Undefined
PASTORINO (no PAH)		9.86	15.43	0.64
PASTORINO (PAH)		15.50	15.32	1.01
KJUUS		19.90	13.04	1.53
BLOT (Georgia)		7.58	6.03	1.26
BLOT (Virginia)		4.87	5.81	0.84
BLOT (Florida)		7.79	10.82	0.72
CHENG		8.43	8.54	0.99
HUILAN		11.06	6.92	1.60
LIDDELL	(a)	0.62	1.01	0.61
	(b)**	0.25	0.65	0.38
ACHESON	(a)	0.00	0.00	Undefined
	(b)**	0.32	0.96	0.33
MEURMAN	(a)	2.08	1.75	1.19
	(b)**	0.54	0.51	1.05
OKSA (Asbestos sprayers)**		1.68	0.00	∞
OKSA (Asbestosis patients)**		1.84	0.00	∞
OKSA (Silicosis patients)**		0.50	0.00	∞
SELIKOFF 2**		1.66	1.36	1.22
BERRY (Men)†	(a)	4.35	0.00	∞
	(b)**	0.43	0.00	∞
BERRY (Women)†	(a)	0.00	0.00	Undefined
	(b)**	0.76	2.41	0.32
SELIKOFF 1**,†		0.75	4.01	0.19

TABLE 5.4 Validity of multiplicative model (cont'd)

Study*	Product of risks for A^-S^- and A^+S^+	Product of risks for A^-S^+ and A^+S^-	Ratio = U
HILT	25.20	0.00	∞
HAMMOND	53.24	56.09	0.95

* For LIDDELL, ACHESON, MEURMAN and BERRY the first estimate (a) uses the data for all four groups, A^-S^-, A^+S^-, A^-S^+ and A^+S^+, while the second estimate (b) uses only the data for the A^+S^- and A^+S^+ groups.

** Assuming SMR in A^-S^- is 0.15 and in A^-S^+ is 1.07

† Dividing smoking specific expected values by 0.15 for S^- and 1.07 for S^+ to make them comparable to same reference population

TABLE 5.5 Testing fit of multiplicative model to case-control data using linear logistic model with binomial error

		Exposure			
Study	Cases	A^-S^-	A^+S^-	A^-S^+	A^+S^+
DEKLERK	Observed	2	4	9	25
	Fitted	1.765	4.235	9.235	24.765
MARTISCHNIG	Observed	28	7	115	51
	Fitted	25.075	9.925	117.925	48.075
RUBINO	Observed	0	0	2	10
	Fitted	0.000	0.000	2.000	10.000
PASTORINO	Observed	7	2	66	31
(no PAH)	Fitted	7.470	1.530	65.530	31.470
PASTORINO	Observed	4	2	42	22
(PAH)	Fitted	3.990	2.010	42.010	21.990
KJUUS	Observed	29	8	103	36
	Fitted	28.99	8.901	103.901	35.099
BLOT	Observed	50	11	313	84
(Georgia)	Fitted	48.715	12.285	314.285	82.715
BLOT	Observed	38	25	186	70
(Virginia)	Fitted	39.153	23.847	184.847	71.153
BLOT	Observed	17	5	208	65
(Florida)	Fitted	17.853	4.147	207.147	65.853
Deviance = 4.507 on 9 d.f.		Not significant			

TABLE 5.6 Testing fit of multiplicative model to cohort data using log linear model with Poisson error

Study	Cases	Exposure A^-S^-	A^+S^-	A^-S^+	A^+S^+
HUILAN	Observed	4	15	11	27
	Fitted	3.017	15.98	11.98	26.02
LIDDELL	Observed	10	11	132	146
	Fitted	12.36	8.636	129.6	148.4
ACHESON	Observed	0	1	0	21
	Fitted	0.00	1.00	0.00	21.00
MEURMAN	Observed	1	1	12	41
	Fitted	0.92	1.081	12.08	40.92
Deviance = 1.646 on 4 d.f.		Not significant			